DE19602985

Publication Title:

Tumour vaccine for treatment of, e.g., carcinoma melanoma or leukaemia

Abstract:

Abstract of DE19602985

Tumour vaccine, for immune therapy of tumours, comprises tumour cells which also contain a gene for an exogenic heat shock protein. Data supplied from the esp@cenet database - Worldwide

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(54) Tumorzellimpfstoff für die Immuntheraphie von malignen Tumoren

(57) Die Erfindung betrifft einen Tumorzellimpfstoff, bei dem die Immunogenität der Tumorzellen durch Einführung des Gens eines exogenen Hitzeschockproteins verstärkt wird. Bevorzugt eingesetzt werden Gene von mikrobiellen Hitzeschockproteinen, die aus Mycobakterien, Escherichia coli oder aus Chlamydia trachomatis erhalten werden.

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Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen

Beschreibung

Die Erfindung betrifft die Herstellung eines gentechnisch modifizierten Tumorzellimpfstoffes für die Immuntherapie von malignen Tumoren. Anwendungsgebiete der Erfindung sind die Medizin und die pharmazeutische Industrie.

Die grundlegende Behandlung von Patienten mit einem soliden malignen Tumor ist die chirurgische oder strahlentherapeutische Entfernung des Primärtumors. Allerdings besteht auch nach kompletter Entfernung des Primärtumors das Risiko, daß Mikrometastasen, die bereits zum Zeitpunkt der Operation existierten, in der postoperativen Phase zu lebensbedrohlichen Metastasen auswachsen. Um die Metastasen zu bekämpfen, wird neben einer chemotherapeutischen Behandlung der Patienten auch versucht, die immunologische Abwehrbereitschaft des Patienten gegen die Tumorzellen wirksam zu stärken. Dies kann durch eine aktive spezifische oder passive Immunisierung geschehen. Die aktive spezifische Immunisierung verfolgt das Ziel, das Immunsystem des Patienten durch Impfung mit devitalisierten Tumorzellen oder definierten tumorassoziierten Antigenen derart zu aktivieren, daß tumorspezifische Abwehrzellen oder Antikörper gebildet werden, die die Mikrometastasen eliminieren oder zumindest deren Wachstum merklich hemmen. Diese Therapieform kann auch zur Behandlung von Patienten mit Leukämie in der Remissionsphase eingesetzt werden. Eine Variante der aktiven spezifischen Immunisierung besteht darin, daß man Immunzellen des Patienten extrakorporal, in der Zellkultur mit Hilfe devitalisierter Tumorzellen oder definierter löslicher tumorassoziierter Antigene tumorspezifisch aktiviert und vermehrt und die derart aktivierten Immunzellen in den Patienten retransfundiert.

Nachteilig für die aktive spezifische Immunisierung ist, daß die Tumorzellen des Menschen in den meisten Fällen eine zu geringe Immunogenität besitzen, um per se eine wirksame immunologische Abwehrreaktion auslösen zu können. Daher ist man darauf angewiesen, die Immunogenität der als Impfstoff vorgesehenen Tumorzellen künstlich zu erhöhen. Dieses kann dadurch geschehen, daß man die Tumorzellen chemisch oder enzymatisch verändert (Prager et. al., Ann NY Acad Sci 276, 61–64 (1976)). Auch ein Hinzufügen apathogener Viren (Cassel et. al, Cancer 52, 856–860 (1983)) oder abgeschwächter Tuberkelbakterien/BCG/(Hanna et. al., Cancer Immunol Immunother 7, 165–173 (1979)) kann die Immunogenität eines Tumorzellimpfstoffes steigern. Mit Hilfe der Gentechnik hat man Gene unterschiedlicher Wirkstoffe in Tumorzellen übertragen, ebenfalls mit der Zielstellung, die von dem Tumorzellimpfstoff ausgelöste Immunantwort zu verstärken (Pardoll, Curr Opin Immunol 4, 619–623 (1992)). Der Gentransfer in Tumorzellen betrifft u. a. Zytokine, Interferone, Kolonie-stimulierende Faktoren, Histokompatibilitätsantigene oder costimulatorisch wirkende Faktoren der Immunantwort, sämtlich Wirkstoffe humaner Herkunft. Trotz mancher Erfolge ist es aber bisher nicht gelungen, einen klinisch überzeugenden Tumorzellimpfstoff zu entwickeln.

Das Ziel der vorliegenden Erfindung ist es, die Immunogenität der als Impfstoff verwendeten Tumorzellen durch gentechnische Modifizierung der Tumorzellen wirksam zu verstärken.

Dieses Ziel wird erfindungsgemäß durch einen Tumorzellimpfstoff erreicht, der aus Tumorzellen besteht, die zusätzlich das Gen eines exogenen Hitzeschockproteins enthalten. Die wichtigste Ausführungsform der Erfindung besteht darin, das Gen eines mikrobiellen Hitzeschockproteins zu verwenden. Bevorzugt ist der Einsatz von Hitzeschockproteinen aus Mycobakterien, Escherichia coli und aus Chlamydia trachomatis. Besonders bevorzugt sind die Hitzeschockproteine HSP 65 und HSP 70 aus Mycobakterien, HSP 70 aus Escherichia coli (DnaK) sowie HSP 60 und HSP 70 aus Chlamydia trachomatis.

Zur Herstellung des Tumorzellimpfstoffes eignen sich autologe Tumorzellen, die mit Hilfe mechanischer oder enzymatischer Methoden aus chirurgisch entferntem Tumorgewebe isoliert werden. Tumorzellinien, die von allogenen Tumoren gleicher Histologie stammen, können ebenfalls verwendet werden, ein Beispiel dafür sind Zellen einer Colonkarzinomlinie. Der Tumorzellimpfstoff wird postoperativ verabfolgt, vor der Applikation werden die Tumorzellen durch radioaktive Bestrahlung devitalisiert.

Mit der Herstellung des erfindungsgemäßen Tumorzellimpfstoffes wird eine neuartige Strategie verfolgt. Durch Einschleusen des Gens eines exogenen Hitzeschockproteins und dessen Expression werden die Tumorzellen nachhaltig verfremdet und damit stärker immunogen. Nach dieser Strategie können Tumorzellimpfstoffe für die Behandlung von Patienten mit Karzinom, Sarkom, malignem Melanom, Leukämie oder malignem Lymphom hergestellt werden.

Patentansprüche

1. Tumorzellimpfstoff für die Immuntherapie von Tumoren bestehend aus Tumorzellen, die zusätzlich das Gen eines exogenen Hitzeschockproteins enthalten.
2. Tumorzellimpfstoff nach Anspruch 1, dadurch gekennzeichnet, daß die Tumorzellen das Gen eines mikrobiellen Hitzeschockproteins enthalten.
3. Tumorzellimpfstoff nach Anspruch 1 und 2, dadurch gekennzeichnet, daß die Tumorzellen das Gen des Hitzeschockproteins HSP65 aus Mycobakterien enthalten.
4. Tumorzellimpfstoff nach Anspruch 1 und 2, dadurch gekennzeichnet, daß die Tumorzellen das Gen des Hitzeschockproteins HSP70 aus Mycobakterien enthalten.
5. Tumorzellimpfstoff nach Anspruch 1 und 2, dadurch gekennzeichnet, daß die Tumorzellen das Gen des Hitzeschockproteins HSP70 aus Escherichia coli (DnaK) enthalten.
6. Tumorzellimpfstoff nach Anspruch 1 und 2, dadurch gekennzeichnet, daß die Tumorzellen das Gen des Hitzeschockproteins HSP60 aus Chlamydia trachomatis enthalten.
7. Tumorzellimpfstoff nach Anspruch 1 und 2, dadurch gekennzeichnet, daß die Tumorzellen das Gen des Hitzeschockproteins HSP70 aus Chlamydia trachomatis enthalten.
8. Tumorzellimpfstoff nach Anspruch 1–7, dadurch gekennzeichnet, daß als Tumorzellen devitalisierte autologe oder allogene Tumorzellen eingesetzt werden.
9. Verwendung des Tumorzellimpfstoffes nach Anspruch 1–8 zur Behandlung von Patienten mit Karzinom, Sarkom, malignem Melanom, Leukämie oder malignem Lymphom.

GB2251186

Publication Title:

Polypeptide for use in treatment of autoimmune disease

Abstract:

Abstract of GB2251186

The use of a polypeptide comprising an amino acid sequence not homologous to a sequence synthesised by the cells of the patient, for the manufacture of a medicament for the treatment of an autoimmune disease is described. Data supplied from the esp@cenet database - Worldwide

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WO 85/05034 A1
Chin.exp.Immunol. 1990. 81, 189-194
Autoimmunity 1990, 7, 237-244
Immunology 1969, 16(2), 157-165

(58) Field of search
UK CL (Edition K) A5B BHA
INT CL^5 A61K 37/02 39/00
Online databases: WPI, DIALOG/PHARM

(54) **Polypeptide for use in treatment of autoimmune disease**

(57) The use of a polypeptide comprising an amino acid sequence not homologous to a sequence synthesised by the cells of the patient, for the manufacture of a medicament for the treatment of an autoimmune disease is described.

GB 2 251 186 A

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2231130

Autoimmune Disease Treatment

This invention relates to the treatment of autoimmune diseases, and especially the prophylactic treatment of such diseases.

Stress of a varied nature, induced as a result of heat shock, nutrient deprivation, oxygen radicals and other forms of metabolic disruption, including infection by certain viruses, bacteria and protozoans, as well as certain cases of cellular transformation, all lead to the increased synthesis of a family of proteins collectively known as stress proteins or heat shock proteins.

These stress proteins are among the most highly conserved and abundant proteins found in nature. Further these proteins have been shown to be among the dominant antigens recognised in immune responses to a broad spectrum of pathogens. A review of the interrelationships between stress proteins, infection and immune surveillance has recently appeared, in which a clear analysis of these relationships is provided (13).

It has become apparent in recent years that a relationship exists between so-called stress or heat shock proteins and certain immune responses to infection and to the development of autoimmunity. As an example, the analysis of cell-mediated and humoral responses to a variety of bacterial and parasitic pathogens has shown that heat shock proteins are often strongly immunogenic during infection (1-8).

Proteins involved in immune responses to certain parasitic diseases such as malaria, shistosomiasis, leishmanisis, trypanosomiasis and filariasis, have been identified as members of the hsp 70 and 90 gene families. Further antigens related to hsp 70 and GroEL families have been shown to play a role in T cell and B cell recognition during bacterial infections including leprosy, tuberculosis and Q. fever. The mycobacterial GroEL stress protein has been identified as the target of a T cell clone capable of causing autoimmune disease in a rat model of adjuvant-induced arthritis (9). Similar results have been obtained as concerns the small heat shock proteins, since an immunologically important 19 Kd protein antigen of Mycobacterium leprae has been sequenced, and shown to have considerable amino acid sequence homology to the soybean 19Kd heat shock protein.

Elevated responses to the GroEL stress protein have been found by testing T cells from synovial infiltrates of rheumatoid arthritis patients (10). Autoantibodies to hsp 90 have been reported in systemic lupus erythrematosus (SLE) (11). In addition, elevated antibody responses to hsp70 and GroEL stress proteins have been found in SLE and in rheumatoid arthritis (12).

The stress proteins are remarkable in their evolutionary conservation: hsp90, hsp70, and hsp60 proteins are found in all prokaryotes and eukaryotes. In fact comparison of almost any two hsp70 proteins from two different organisms indicates an amino acid homology of around 50%. The major stress proteins occur at low levels in normal, unstressed cells, but accumulate to very high levels in cells undergoing stress. A striking example is the case of E. coli hsp60, which accounts for 1.6% of total cell protein under normal growth conditions, and can accumulate to 15% of total cell protein after heat shock (14). Stress proteins appear to fulfil vital roles in cells, both in the absence and in the presence of stress. They appear to be involved in the assembly and disassembly of protein complexes, and hsp70 proteins are important for the translocation of certain proteins through cellular membranes (15). Stress proteins appear to interact with many different proteins, for example, hsp90 has been found to interact with steroid hormone receptors and with viral and cellular kinases. Hsp70 proteins bind to DNA replication complexes, clathrin baskets, the cellular tumour antigen p53, and immunoglobulin heavy chains. Plant hsp60 interacts with Rubisco, which fixes CO_2 in chloroplasts, and may be the most abundant protein in the biosphere (16). The interaction of stress proteins with multiple proteins may provide an explication for the evolutionary constraints imposed on their amino acid sequences.

Stress proteins have an almost certain role in protecting cells and organisms from the deleterious effects of heat and other stresses.

It seems clear that the tight sequence regulation imposed on many heat shock protein sequences throughout evolution has led to such retained sequences between those of the host and those of the infectious agent having a significant degree of identity. Clearly the reaction of the host immune system against antigens of the infecting organism could lead to the raising of antibodies against heat shock proteins. The sequence homology within the heat shock protein family thus points to conserved sub-sequences of heat shock proteins as being serious candidates for inducing an immune response that can have specificity against self sequences, with the consequence of inducing an autoimmune reaction and the associated disease states.

The reports referenced above indicate that stress proteins, such as the heat shock proteins, provide particularly attractive targets for immune recognition. An analysis the cross reactivity of T cell responses to stress proteins has been published recently (17), wherein the presence of human T cells was demonstrated that were capable of immune recognition of conserved sequence determinants. These authors have proposed a model in which immune responses to stress proteins provide a link between infectious and autoimmune diseases.

Although models of the role of stress proteins in autoimmune diseases have been proposed, no-one has yet suggested possible treatment for autoimmune diseases.

In accordance with a first aspect of the present invention a method of treating an autoimmune disease in a patient comprises introducing a compound, comprising

an amino acid sequence of a protein which is not homologous with amino acid sequences synthesised by cells of the patient, into the patient.

In accordance with another aspect of the present invention there is provided use of a compound comprising an amino acid sequence of a protein for the treatment of an autoimmune disease in a patient, wherein the amino acid sequence is not homologous with amino acid sequences synthesised by cells of the patient.

Further, the invention provides a composition for treatment of an autoimmune disease in a patient, comprising a compound which comprises an amino acid sequence of a protein which is not homologous with amino acid sequences synthesised by cells of the patient, in combination with a pharmaceutical carrier.

Still further, the invention provides the use of a compound comprising an amino acid sequence of a protein which is not homologous with amino acid sequences synthesised by the cells of a patient for the manufacture of a medicament for the treatment of an autoimmune disease in the patient.

Preferably, the compound comprises a peptide which comprises the amino acid sequence and typically, the protein is a stress or heat shock protein.

Preferably, the treatment is prophylactic.

Typically, the compound could be introduced into a patient by incorporation in a cream or ointment, in a soluble glass, in slow release capsules, transdermal

patches, injected, or even administered orally or in suppository form.

Preferably, the amino acid sequence has antigenic properties.

The amino acid sequence could be naturally occurring or be synthesised. If the amino acid sequence is synthesised then the peptide could comprise a number of different amino acid sequences and/or multiples of the same amino acid sequence.

The invention described here is based on the above-detailed conservation of heat shock sequences and their implication in autoimmune diseases. Contrary to the identity of certain conserved sequences, this invention, is based on the hypervariable sequences of stress proteins. Prior immunisation with natural or synthetic peptides representing such non-conserved, variable or hypervariable stress protein sequences of origin from infectious agents of bacterial and other parasitic pathogens, induces antibody responses against the stress proteins of the infecting organism, and these specifically induced antibodies are incapable of recognising self stress protein sequences. The rapid recognition of infectious agent - specific stress proteins by specific pre-existing antibodies raised against non-homologous peptides from invading stress proteins should allow the elimination of these stress proteins before they are able to elicit potentially autoimmune responses.

This invention concerns the immune recognition of peptide epitopes of specific heat shock or stress proteins, and the development of peptide-based therapy

or prevention based on such epitopes.

Examples of the invention will now be described.

1. Analysis of stress protein peptide sequences

In order to practice the preventive/therapeutic approach described in this invention, it is necessary to examine in detail the amino acid sequences of human heat shock proteins, and of those of organisms infecting human beings with whom correlations of immune diseases exist.

Our initial approach was to assemble a table of certain of the known sequences of stress proteins from human and infectious agent sources. A selection of these sequences are presented in Appendix 1. A thorough analysis of sequence homology between members of each of the stress protein families indicates that for each of the principle stress protein families, hsp70, hsp90 and hsp27, certain sequences have been highly conserved throughout evolution, whereas parts of the stress proteins contain amino acid sequences that are highly differentiated. One assumes that the conservational pressures concerning the retained sequences are associated with critical structural or functional aspects of these important proteins. The variable regions are presumably of less critical structural or functional importance, thus escaping from the conservative pressure/selection activities prevailing in evolving organisms.

2. Selection of candidate peptide vaccines

The selection of useful candidate peptides capable of eliciting an immune response specifically against the stress proteins of the infectious agent is based on two major criteria:

i) The non-identity of selected peptide sequences, and their lack of resemblance to highly, or partially conserved stress protein sequences, common to human and infectious agent proteins. The selection of such non-conserved sequences is derived from a reverse analysis of amino acid sequence homologies, in other words, concentrating on the non-homologous sequences evident from homology analyses such as those shown in (1) and in appendix 2.

For a thorough selection of sequence differences versus sequence homology, it is instructive to, in addition to amino acid identity, to look at replacements by highly conserved amino acids. Examples of such substitutions are the following groups: (aspartic acid and glutamic acid), (lysine and arginine), (serine and threonine), (phenylalanine and tyrosine), and (isoleucine, leucine, valine and methionine).

ii) An analysis of the antigenic potential of selected peptide sequences. Where information is available, peptide epitopes that conform to the criteria of both points i) and ii), and which can be demonstrated to be immunodominant, are preferred examples of the preventive/therapeutic peptides described in this invention.

Examples of the amino acid sequences of some selected peptides that reply to the criteria of point i) are

presented in appendix 2.

Examples of group i) peptides that are expected to have considerable immunogenic potential have been selected on the basis of presently accepted criteria of immunological potential. Examples of certain peptides with pronounced antigenicity are shown in appendix 3.

Non-homologous sequence comparison of the known stress protein and related antigen sequences from humans and from infectious agents has been performed. In the case of <u>Plasmodium</u> <u>falciparum</u>, in addition to regions of extensive homology of amino acid sequence between the two proteins, clear regions of extensive lack of homology are also detectable, and the following sequence fragments, depicted using the one and three-letter amino acid abbreviations derived from the IUPAC-IUB Commission on Biochemical Nomenclature (see Table 1), illustrate this example:-

ALIGNMENT OF RESIDUES 133 TO 254 OF 75KDa antigen of <u>P</u> <u>Falciparum</u> TO RESIDUES 357 TO 635 OF HSP70 HUMAN

ENYCYGVKSSLEDKIKEKLQPAEIETCMKTITTILEWLEKNQLAGKDEYE
------------ **KNALES-Y-AFNMKSA- VEDEG LKGKIS-E**

AKQKEAESVCAPIMSKIY-QDAA-**GAAGGMPGGM-P-GGMPGGMP** GGMNF
ADKKKVLDKCQEVIS- WLDANTLA **EKDEFEHKRKELEQVCNPIISGL-Y**

PG-GMPG-AGMPGNAP---AGSGPTVEEVV
QGAGGPGPGGFGAQGPKGGSGSGPT-----

Examples of non-homologous peptides are shown in bold letters. The second peptide of HSP70 human shown in

bold above, denoted "Peptide example 1", has been compared to the sequence of the corresponding antigen of <u>Mycobacterium</u> <u>tuberculosis</u> and its highly unique sequence has little or no counterpart in the sequence of tubercular origin.

ALIGNMENT OF RESIDUES 8 TO 11 OF PEPTIDE 1 TO RESIDUES 1 TO 127 OF 71KDa antigen <u>M.tuberculosis</u>

```
K----R--K--    E-----------------------------------
KEDIDRMIKDAEAHAEEDRKRREEADVRNGAETLVYNTEKFVKEQREGG
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Clearly other peptide sequences unique to an infectious agent antigen exist and will have value in the applications described in this invention. In order to identify such sequences, extensive cloning, expression and sequence analysis of infectious agent antigens will be required. Such research, although technically arduous, is quite within the realms of existing technology. Similarly, once new sequences are established, the presence or absence of amino acid sequence homologies can be determined either visually, or through the use of any number of amateur or commercial sequence analysis software programs. Our intention here is to demonstrate the general procedure for identifying, and applying both specific non-homologous and specific homologous stress and infectious agent antigen peptide sequences to the vaccination, therapeutic and cosmetic applications described herein.

<u>3 The Rational Design of Synthetic Peptides</u>

This invention is not limited to naturally occurring variant sequences within stress proteins, nor is it limited to the selection and use of a single variant epitope. For example, synthetic peptides could be used. In addition, the peptide could be synthesised to have combinations of different variant sequences or multiples of variant sequences. By synthesising peptides comprising different variant sequences and/or multiples of the same variant sequence it may be possible to design peptides having a stronger immune response against stress proteins of infectious organisms but which do not recognise human stress epitopes.

A recent analysis of variant peptide epitopes of myelin basis protein (MBP), and their influence on the incidence of experimental autoimmune encephalomyelitis (EAE) has indicated that synthetic variants of an N-terminal MBP peptide can have greatly altered properties of binding to cell surface glycoproteins encoded by the major histocompatibility complex (MHC) (18). In other words, the efficacy of the complex interactions associated with the elicitation of an effective immune response against peptide antigens, can be altered and improved in some cases, by the use of synthetic variants of natural antigens. The subject of this invention comprises those variant peptide sequence approaches that are taught by the authors of reference 18, amongst others.

An efficient mapping procedure for identifying protein antigenic determinants has been described that would be of use in the selection of useful antigenic determinants for the applications taught in this invention (19). Clearly classical chemical, enzymatic

and combined synthetic procedures can be utilised to produce candidate peptides, once identified and selected, for the vaccine applications described here. A naturally expected limitation of the peptide vaccines that can be produced using this described procedure derives from the fact that about one third of monoclonal and polyclonal antibodies made by immunising with native protein react with assembled topographic sites (20). These assembled determinants may not form the appropriate structure outside of a proteins native environment. This limitation is not expected to significantly limit the practical use of this invention.

Studies concerning T Cell recognition and activation have indicated that it may be possible to design peptides with predictable and advantageous properties (21). These authors have described two approaches for immunomodulation that could be useful for the design of therapeutic strategies against autoimmune encephalomyelitis. The first approach consists of a thorough molecular characterisation of an encephalitogenic epitope, and the subsequent design of peptide analogs that retain normal or increased major histocompatibility complex binding properties, and that fail to activate disease-inducing T cells. Secondly, novel properties of a heterocyclic peptide have been described, with the result that the peptide is highly antigenic _in vitro_, while being non-immunogenic _in vivo_. These authors have been able to demonstrate the feasibility of immune intervention in an immune disease through the use of a synthetic peptide. These results are complementary to the procedure we describe here, but are not identical, nor do they in any way predict the approach that we describe.

4 Applications of the stress protein peptides described herein

The basic tenant that we have developed herein is based on the multiple observations that certain infectious agent antigens are closely related in amino acid sequence to human stress proteins, and that immune reactions against such antigens can cross react with the human proteins, leading to the possibility of developing autoimmune disease. Our invention describes the selection of stress protein peptide sequences from infectious agent antigens related to human stress proteins, but which have little or no sequence homology within such human stress proteins. The injection of such non-homologous peptides into human beings, for instance in an emulsification with Freunds complete adjuvant, would provide a route of effective vaccination against subsequent autoimmune disease induced as mentioned above. The antibodies raised through such vaccination are specific to the selected infectious agent antigen from which the vaccinating peptide was derived. Such induced antibodies are specific tc infectious agent antigens, thus explaining their efficacy in the application of this invention.

Further, since the vaccinating agent is a small peptide, instead of a large, complex protein such as human factor VIII, or factor IX, it is not compulsory to use an injection as a means of delivering the peptide to a human subject. We thus reserve in our application the administration of the kinds of peptides described by transdermal applications, a number of which are presently commercialised with considerable success.

Further still, since certain major diseases that are thought to have their origin in autoimmune diseases, such as arthritis and rheumatism, the peptides of this invention can be applied externally, in both local and cosmetic application to painful joints and articulations resulting from these prevalent diseases.

For example, the peptides could be administered to a patient by incorporation in a cream or ointment, in a soluable glass, in slow release capsules, transdermal patches, injected, or even administered orally or in suppository form.

In addition, due to the nature of amino acid sequences it is unlikely that treatment using these substances will produce the unpleasant side effects which are normally associates with drugs.

APPENDIX 1

NON-HOMOLOGOUS SEQUENCES WHICH ARE ALSO KNOWN ANTIGENICS ARE DENOTED BY UNDERLINING AND NON-HOMOLOGOUS ONLY SEQUENCES ARE DENOTED BY BOLD LETTERING

SEQUENCE OF HUMAN STRESS PROTEINS

A) Sequence HSP90 Human

Rebbe N F, Ware J, Bertina M, Modrich P, Stafford D W
Gene 53:235-245(1987)
EMBL; M16660; HSHSP90
KW Heat Shock. Sequence 724 AA; 83293 MW

MPEEVHHGEE	EVETFAFQAE	IAQLMSLIIN	TFYSNKEIFL	40
RELISNASDA	LDKIRYESLT	DPSKLDSGKE	LKIDIIPNPQ	80
ERTLTLVDTG	IGMTKADLIN	NLGTIAKSGT	KAFMEALQAG	120
ADISMIGQFG	VGFYSAYLVA	EKVVVIRKHN	DDEQYAWESS	160
AGGSFTVRAD	HGEPIGMGTK	VILHLKEDQT	EYLEERRVKE	200
VVKKHSQFIG	YPITLYLEKE	REKEISDDEA	EEEKGEKEEE	240
DKDDEEKPKI	EDVGSDEEDD	SGKDKKKKTK	KIKEKYIDQE	280
ELNKTKPIWT	RNPDDITQEE	YGEFYKSLTN	DWEDHLAVKH	320
FSVEGQLEFR	ALLFIPRRAP	FDLFENKKKK	NNIKLYVRRV	360
FIMDSCDELI	PEYLNFIRGV	VDSEDLPLNI	SREMLQQSKI	400
LKVIRKNIVK	KCLELFSELA	EDKENYKKFY	EAFSKNLKLG	440
IHEDSTNRRR	LSELLRYHTS	QSGDEMTSLS	EYVSRMKETQ	480
KSIYYITGES	KEQVANSAFV	ERVRKRGFEV	VYMTEPIDEY	520
CVQQLKEFDG	KSLVSVTKEG	LELPEDEEEK	KKMEESKAKF	560
ENLCKLMKEI	LDKKVEKVTI	SNRLVSSPCC	IVTSTYGWTA	600

NMERIMKAQA	LRDNSTMGYM	MAKKHLEINP	DHPIVETLRQ	640	
KAEADKNDKA	VKDLVVLLFE	TALLSSGFSL	EDPQTHSNRI	680	
TYMIKLGLGI	DEDEVAAEEP	NAAVPDEIPP	LEGDEDASRM	720	
EEVD				724	

B) Sequence HSP70 Human

[1] Hunt C, Morimoto R I;
Proc Natl Acad Sci USA 82:6455-6459(1985)
EMBL; M11236; HSHSP701
EMBL; MII717; HSHSP70D
KW Heat Shock
Sequence 640AA; 69867 MW

MAKAAAVGID	LGTTYSCVGV	FQHGKVEIIA	NDQGNRTTPS	40	
YVAFTDTERL	IGDAAKNQVA	LNPQNTVFDA	KRLIGRKFGD	80	
PVVQSDMKHW	PFQVINDGDK	PKVQVSYKGE	TKAFYPEEIS	120	
SMVLTKMKEI	AEAYLGYPVT	NAVITVPAYF	NDSQRQATKD	160	
AGVIAGLNVL	RIINEPTAAA	IAYGLDRTGK	GERNVLIFDL	200	
GGGTFDVSIL	TIDDGIFEVK	ATAGDTHLGG	EDFDNRLVNH	240	(3)
FVEEFKRKHK	KDISQNKRAV	RRLRTACERF	EGIDFYTSIT	280	
RARFEELAKR	TLSSSTQASL	EIDSLCSDLF	RSTLEPVEKA	320	(4)
LRDAKLDKAQ	IHDLVLVGGS	TRIPKVQKLL	QDFFNGRDLN	360	
KSINPDEAVG	YGAAVQAAIL	MGDKSENVQD	LLLLDVAPLS	400	
LGLETAGGVM	TALIKRNSTI	PTKQTQIFTT	YSDNQPGVLI	440	
QVYEGERAMT	KDNNLLGRFE	LSGIPPAPGV	PQIEVTFDID	480	(1)
ANGILNVTAT	DKSTGKANKI	TITNDKGRLS	KEEIERMVQE	520	
AEKYKAEDEV	QRERVSAKNA	LESYAFNMKS	AVEDEGLKGK	560	(2)
ISEADKKKVL	DKCQEVISWL	DANTLAEKDE	FEHKRKELEQ	600	
VCNPIISGLY	QGAGGPGPGG	FGAQGPKGGS	GSGPTIEEVD	640	

C) Sequence Human HSP27

Hickey E, Brandon S E, Potter R, Stein G, Stein J, Weber L A;
Nucl. Acids Res 14:4127-4145(1986)
EMBL;X03900; HSHSP27
KW: HEAT SHOCK
SEQUENCE 199 AA; 22327 MW;

MTERRVPFSL	LRGPSWDPFR	DWYPHSRLFD	QAFGLPRLPE	40
EWSQWLGGSS	WPGYVRPLPP	AAIESPAVAA	PAYSRALSRQ	80
LSSGVSEIRH	TADRWRVSLD	VNHFAPDELT	VKTKDGVVEI	120
TGKHEERQDE	HGYISRCFTR	KYTLPPGVDP	TQVSSSLSPE	160
GTLTVEAPMP	KLATQSNEIT	IPVTFESRAQ	LGGRSCKIR	200

D) Sequence Human HSP60

Sequence not yet available, submitted for publication: Gupta R S, Jinal S, Harley C B and Dudani A K(1989)

SEQUENCE OF HSP60 YEAST

Reading D S, Hallberg R L and Myers A M (1989). Nature 337 655

MLRSSVVRSR	ATLRPLLRRA	YSSHKILKFG	VIGRASLLKG	40
VETLAIAVAA	TLGPKGRNVL	IEQPFGPPKI	TKDGVTVAKS	80
IVLKDKFINM	GAKLLQIVAS	KTNIAAGDGT	TSATVLGRAI	120
FTISVKNVAA	GCNPMDLRRG	SQVAVIKVIL	FLSANKKEIT	160
TSEEIAQVAT	ISANGDSHVG	KLLASAMEKV	GKEGVITIRE	200
GRITLEDELE	VTEGMRFDRG	FISPYFITDP	KSSKVEFEKP	240
LLLLSEKKIS	SIQDILPALE	ISNQSRRPLL	IIAEDVDGEA	280
LAACILNKLR	GQVKVCAVKA	PGFGDNRKNT	IGDIAVLTGG	320

TVFTEELDLK	PEQCTIENLG	SCDSITVTKE	DTVILNGSGP	360
KEAIQERIEQ	IKGSIDITTT	NSYEKEKLQE	RLAKLSGGVA	400
VIRVGGASEV	EVGEKKDRYD	DALNATRAAV	EEGILPGGGT	440
ALVKASRVLD	EVVVDNFDQK	LGVDIIRKAI	TRPAKQIIEN	480
AGEEGSVIIG	KLIDEYGDDF	AKGYDASKSE	YTDMLATGII	520
DPFKVVRSGL	VDASGVASLL	ATTEVAIVDA	PEPPAAAGAG	560
GMPGGMPG	MPGMM			600

SEQUENCES OF BACTERIAL ANTIGENS

A) Mycobacterium leprae

18 KDa Antigen

Nerland A H, Mustapha A S, Sweetser D, Godal T, Young R
J Bacteriol 170 5919-5921 (1988)
Sequence 148 AA; 16643MW;

MLMRTDPFRE	LDRFAEQVLG	TSARPAVMPM	DAWREGEEFV	40
VGFDLPGKA	DSLDIDIERD	VVTVRAERPG	VDPDREMLAA	79
ERPRGVFNRQ	LVLGENLDTE	RILASYQEGV	LKLSIPVAER	119
AKPRKISVDR	GNNGHQTINK	TPHEIIDA		

65 KDa Antigen

Mehra V, Sweetser D and Young R A (1986) Proc Natl Acad Sci USA 83 7013

AA 589, MW 61,831
The Underling Amino Acids Correspond To Antigenic Peptides.

VPGRDGETQP	ASCGRPSRAL	HPASVSNGGC	RSPVILASFL	40
IRRNHFAMAK	TIAYDEEARR	GLERGLNSLA	DAVKVTLGPK	80
GRNVVLEKKW	GAPTITNDGV	SIAKEIELED	PYEKIGAELV	120
KEVAKKTDDV	AGDGTTTATV	LAQALVKEGL	RNVAAGANPL	160
GLKRGIEKAV	DKVTETLLKD	AKEVETKEQI	AATAAISAGD	200
QSIGDLIAEA	MDKVGNEGVI	TVEEESNTFG	LQLELTEGMR	240
FDKGYISGYF	VIDAERQEAV	LEEPYILLVS	SKVSTVKDLL	280
PLLEKVIQAG	KSLLIIAEDV	EGEALSTLVV	NKIRGTFKSV	320
AVKAPGFGDR	RKAMLQDMAI	LTGAQVISEE	VGLTLENTDL	360
SLLGKARKVV	MTKDETTIVE	GAGDTDAIAG	RVAQIRTEIE	400
NSDSDYDREK	LQERLAKLAG	GVAVIKAGAA	TEVELKERKH	440
REIDAVRNAK	AAVEEGIVAG	GGVTLLQAAP	ALDKLKLTGD	480
EATGANIVKV	ALEAPLKQIA	FNSGMEPGVV	AEKVRNLSVG	520
HGLNAATGEY	EDLLKAGVAD	PVKVTRSALQ	NAASIAGLFL	560
TTEAVVADKP	EKTAAPASDP	TGGMGGMDF		600

70 KDa Antigen

Not yet sequenced. Immunological cross-reactivity with the 71 KDa antigen of Mycobacterium tuberculosis (YOUNG ET AL Proc Natl Acad Sci USA 85, 4267-4270 (1988).

B) Mycobacterium tuberculosis

65 KDa Antigen

Schinnick, T S (1987). Journal of Bacteriology 169 1080

AA 562, MW 59083

RGCRHPVTPP VSSPIRRNHF AMAKTIAYDE EARRGLERGL 40
NALADAVKVT LGPKGRNVVL EKKWGAPTIT NDGVSIAKEI 80
ELETPYEKIG AELVKEVAKK TDDVAGDGTT TATVLAQALV 120
REGLRNVAAG ANPLGLKRGI EKAVEAKVTET LLKGAKEVET 160
KEQIAATAAI SAGDQSIGDL IAEAMDKVGN EGVITVEESN 200
TFGLQLELTE GMRFDKGYIS GYFVTDPERQ EAVLEDPYIL 240
LVSSKVSTVK DLLPLLEKVI GAGKPLLIIA EDVEGEALST 280
LVVNKIRGTF KSVAVKAPGF GDRRKAMLQD MAILTGGQVI 320
SEEVGLTLEN ADLSLLGKAR KVVVTKDETT IVEGAGDTDA 360
IAGRVAQIRQ EIENSDSDYD REKLQERLAK LAGGVAVIKA 400
GAATEVELKE RKHRIEDAVR NAKAAVEEGI VAGGGVTLLK 440
AAPTLDELKL EGDEATGANI VKVALEAPLK QIAFNSGLEP 480
GVVAEKVRNL PAGHGLNAQT GVYEDLLAAG VADPVKVTRS 520
ALQNAASAIG LFLTTEAVVA DKPEKEKASV PGGGDMGGMD 560
F 600

71 KDa Antigen

Partial sequence, contains only the homolgy domain with HSP70

Young D, Lathigra R, Hendrix R, Sweetser D, Young R, Proc Acad Sci USA 85, 4265-4270 (1988).

EFQPSVQIQV YQGEREIAAH NKLLGSFELT GIPPAPRGIP 40 (1)
QIEVTFDIDA NGIVHVTAKD KGTGKENTIR IQEGSGLSKE 80
DIDRMIKDAE AHAEEDRKRR EEADVRNGAE TLVYNTEKFV 120 3,4
KEQREGGSKV PEDTWRIGYF GHQVGDGEAG PGVAGSGASD 160 (2)
LRSSSGCVTG HWRCPPRAAA GRCPPRLGM 200

C) Plasmodium falciparum (MALARIA)

90 KDa Antigen

M Jendoubi, S Bonnefoy, Nucl Acids Res 16, 10928 (1988) Partial sequence, contains only the region of homology with HSP90

KDFDGKKLKC	CTKEGLDIHH	SEEAKKDFET	VIKDVLHKKV	40
EKVVVCQRIT	DSPCVLVTSE	FGWSANMERI	MKAQALRDNS	80
MTSYMLSKKI	MEINARHPII	SALKQKADAD	KSDKTVKYLI	120
WLLFDTSLLT	SGFFALEEPT	TFSKRIHRMI	KLGLSIDEEE	160
NNDIDLPPLE	ETVDATDSKM	EEVD		200

75 KDa Antigen

Ardeshir F, Flint J E, Richman S and Reese R T, Embo J. 6, 493-499 (1987).
Partial sequence from the first AA

MLKLIERNTT	IPAKKSQIFT	TYADNQPGVL	IQVYEGERAL	40
TKDNNLLGKF	HLDGIPPAPR	KVPQIEVTFD	IDANGILDVT	80
AVEKSTGKQN	HITITNDKGR	LSQDEIDRMV	NDAEKYLAED	120
EENRKRIEAR	NSLENYCYGV	KSSLEDKIKE	KLQPAEIETC	160
MKTITTILEW	LEKNQLAGKD	EYEAKQKEAE	SVCAPIMSKI	200
YQDAAGAAGG	MPGGMPGGMP	GGMPGGMNFP	GGMPGAGMPG	240
NAPAGSGPTV	EEVVD			280

APPENDIX 2

DIFFERENTIATION OF HOMOLOGOUS (UNDERLINE)
AND NON-HOMOLOUGOS SEQUENCES

A) Alignment of Residues 47 to 161 of partial sequence of P.Falciparum 90KD to residues 581 to 699 of human HSP90

--RI-DSPCVLVTSEFGWSANMERIMKAQALRDNSMTSYMLSKKIMEINAR
NRLVSSPCCIVTSTYGWTANMERIMKAQALRDNSTMGYMMAKKHLEINPD

HPIISALKQKADADKSDKTVKYLIWLLFDTSLLTSGFFALEEPTTFSKRI
HPIVETLRQKAEADKNDKAVKDLVVLLFETALLSSG-FSLEDPQTHSNRI

HRMIKLGLSIDEEE---NN
YRMIKLGLGIDEDEVAAEE

B) Alignment of residues 7 to 157 of partial sequence of P. falciparum 70 KDa to residues 411 to 613 of human HSP70.

-----NTTIPAKKSQIFTTYADNQPGVLIQVYEGERALTKDNNLLGKFHL
ALIKRNSTIPTKQTQIFTTYSDNQPGVLIQVYEGERAMTKDNNLLGRFEL

DGIPPAPRKVPQIEVTFDIDANGILDVTAVEKSTGKQNHITITNDKGRLS
SGIPPAP-GVPQIEVTFDIDANGILNVTATDKSTGKANKITITNDKDRLS

QDEIDRMVNDAEKYLAEDEENRKRIEARNSLENYCYGVKSSLEDK-IKEKLQ
KEEIERMVQEAEKYKAEDEVQRERVSAKNALESYAFNMKSAVEDEGLKGKIS

PAETCMK---TITTILEWLEKNQLAGKDEYEAKQKEAESVCAPIMSKIYQDA
EADKKKVLDKCQEVI-SWLDANTLAEKDEFEHKRKELEQVCNPIISGLYQGA

C) Alignment of residues 5 to 110 of M tuberculosis 71K to residues 430 to 548 of human HSP70

```
-------VQIQVYQGEREIAAHNKLLGSFELTGIPPAPRGIPQIEVTFDI
YSDNQPGVLIQVYEGERAMTKDNNLLGRFELSGIPPAP-GVPQIEVTFDI

DANGIVHVTAKDKGTGKENTIRIQEGSG-LSKEDIDRMIKDAEAHAEEDR
DANGILNVTATDKSTGKANKITITNDKGRLSKEEIERMVQEAEKYKAEDE

KRREEADVRNGAE------
VQRERVSAKNALESYAFNM
```

APPENDIX 3

Antigenic Peptides of the 65 Kda Antigen of *Mycobacterium leprae*

MEHRA V, SWEETSER D and YOUNG R A (1986) Proc Natl Acad Sci USA 83 7013

-NSLADAVKVTLGPKGRNVVLEKKWGAPTITNDGVS
-RNVAAGANPLGLKRGIEKAV
-ALDKLKLTGDEATGA
-GEYEDLLKAGVADP
-ASDPTGGMGGMDF

TABLE 1

One and Three Letter Amino Acid Abbreviations

A	Ala	Alanine
C	Cys	Cysteine
D	Asp	Aspartic acid
E	Glu	Glumatic acid
F	Phe	Phenylalanine
G	Gly	Glycine
H	His	Histidine
I	Ile	Isoleucine
K	Lys	Lysine
L	Leu	Leucine
M	Met	Methionine
N	Asn	Asparagine
P	Pro	Proline
Q	Gln	Glutamine
R	Arg	Arginine
S	Ser	Serine
T	The	Threonine
V	Val	Valine
W	Trp	Tryptophane
Y	Tyr	Tyrosine
B	Asx	Asp or Asn (not distinguished)
Z	Glx	Glu or Gln (not distinguished)
X	X	Undetermined or atypical amino acid

From: IUPAC-IUB Commission on Biochemical Nomenclature, J Biol Chem 243, 3557-3559, 1968.

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CLAIMS

1. A method of treating an autoimmune disease in a patient comprises introducing a compound, comprising an amino acid sequence of a protein which is not homologous with amino acid sequences synthesised by cells of the patient, into the patient.

2. Use of a compound comprising an amino acid sequence of a protein for the treatment of an autoimmune disease in a patient, wherein the amino acid sequence is not homologous with amino acid sequences synthesised by cells of the patient.

3. A composition for treatment of an autoimmune disease in a patient, comprising a compound which comprises an amino acid sequence of a protein which is not homologous with amino acid sequences synthesised by cells of the patient, in combination with a pharmaceutical carrier.

4. The use of a compound comprising an amino acid sequence of a protein which is not homologous with amino acid sequences synthesised by the cells of a patient for the manufacture of a medicament for the treatment of an autoimmune disease in the patient.

Patents Act 1977
Examiner's report to the Comptroller under Section 17 (The Search Report)

Application number
9026278.3

Relevant Technical fields

(i) UK Cl (Edition K) A5B(BHA)

(ii) Int Cl (Edition 5) A61K 39/00, 37/02

Databases (see over)

(i) UK Patent Office

(ii) ONLINE DATABASES:WPI, DIALOG/PHARM

Search Examiner

C SHERRINGTON

Date of Search

3 FEBRUARY 1992

Documents considered relevant following a search in respect of claims

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
X	GB 2221157 A (BIOGAL GYOGYSZERGYAR) especially page 1,line 12-14; Claim 19	4
X	EP 0322990 A1 (DE STAAT DER NEDERLANDEN..) whole document	4
X	WO 88/10120 A1 (BRIGHAM AND WOMEN'S HOSPITAL) whole document especially page 6, line 19 - page 7, line 3; Example 6; Claims 1-10,13-19	4
A	WO 85/05034 A1 (UNIVERSITY OF LONDON ET AL) especially page 2, line 18 - page 3, line 4; Claims 3-5	4
X	Clin.exp.Immunal.1990,81,189-194 Prevention of adjuivant arthritis in rats by a nonapeptide from the 65-kd...	4
X	Autoimmunity 1990,7,237-244 The immune response to Mycobacterial heat shock proteins	4
X	Immunology 1969,16(2),157-165 Inhibition of Adjuvant Arthritis by Protein Antigens	4

Category	Identity of document and relevant passages	Relevant to claim(s)

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